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(57) Abstract

There is disclosed use of one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof to treat pruritus (itching), preferably by topical administration. A non-therapeutic method of cosmetic treatment (to prevent disfigurement by suppressing the urge to scratch the itchy site) is also disclosed. Pharmaceutical compositions for this treatment are described which comprise these NSAIDs and/or their salts as an anti-pruritic agent, preferably the only anti-pruritic agent. Preferably, the anti-pruritic agent comprises from about 0.01 % to about 25 % by weight of the composition. Use of these NSAIDs and/or salts in the preparation of a medicament for treating pruritus is also disclosed.

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NSAIDs IN THE TREATMENT OF PRURITUS

The present invention relates to use of various specified non steroidal anti-inflammatory drugs (hereinafter referred to as NSAIDs) and/or one or more of their pharmaceutically acceptable salt or salts for treating pruritus. The specified NSAIDs and/or their pharmaceutically acceptable salt or salts may be administered topically.

Pruritus, or itching, is an unpleasant condition of the skin surface. Although pruritus is a complex phenomena, it may be defined crudely as the skin sensation which evokes the motor response of scratching. The causes of pruritus are due to many different conditions. Some causes are local and can easily be removed, for example slight mechanical irritation such as contact with rough, woollen underclothing, or parasites such as lice or scabies. Some causes of pruritus are more general and can result in a condition which is chronic.

In pruritic conditions, examples of which are described hereinafter, itching may be so constant as to be unbearable. Often the habit of scratching can be acquired, which in the course of time renders the skin rough and thickened, and this of itself aggravates and keeps up the itchiness. Sometimes the condition becomes so chronic and the skin is so changed by scratching that the pruritus becomes incurable.

It can be seen therefore that alleviation of the symptoms of pruritus is very important in its treatment both to reduce discomfort and to discourage scratching. Notwithstanding that in many cases complete cure will only be effected by treatment of the underlying condition, for example diabetes mellitus, it is nevertheless desirable to treat the pruritus directly as well as its underlying cause.

Most non-steroidal anti-inflammatory drugs (NSAIDs) are known to have anti-inflammatory, antipyretic and/or analgesic activity. Therefore known uses of NSAIDs include the treatment of pain and inflammation in musculoskeletal disorders such as rheumatic disease, and the treatment of pain in a variety of other disorders, for example headache, neuralgia and dysmenorrhoea. Some NSAIDs may have been used as an active ingredient in a topical composition to treat some or all of these known indications.

The state of the art at the earliest priority date of the present invention is now discussed.

International application WO 92/22585 (Patent Biopharmaceutics Inc.) discloses a composition for treating the symptoms of haemorrhoids and other anorectal diseases (which includes, inter alia, pruritus) using hyaluronic acid as the sole anti-pruritic ingredient. A disclosure that any, unspecified anti-inflammatory agent might be added as an additional optional ingredient to this composition does not suggest that the anti-inflammatory agent would have any other activity, or would be added for any other purpose than optionally to add anti-inflammatory properties to the anti-pruritic composition.

The abstract of United States patent 3,686,183 (Syntex Corp.) asserts:

'The substituted arylacetic acids are useful as anti-inflammatory, analgesic, anti-pyretic and anti-pruritic agents'.

This document makes no further reference to anti-pruritic activity of these compounds. The invention claimed in US 3,686,183 relates to a process for producing racemic mixtures of substituted arylacetic acids. Specific compounds claimed and described are naphthalene acetic acids. US 3,686,183 does not describe any experiments or produce any data to support the incidental assertion in the abstract of anti-pruritic activity in relation to a broad general

class of compounds. This reference in the abstract must be considered highly speculative and is not supported by the document which it abstracts.

The applicant's patent application WO 95/11017 describes use of ibuprofen and/or flurbiprofen to topically treat pruritus.

There is no explicit reference in the prior art to use of any of the specific NSAIDs disclosed herein to treat pruritus.

The applicants have now discovered that the NSAIDs: bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof, are useful as anti-pruritic agent or agents in the treatment and alleviation of the symptoms of pruritus. Preferably these NSAIDs are administered topically. Hereinafter the term "specified NSAIDs" refers to the preceding list of NSAIDs.

Therefore broadly according to the present invention there is provided use of one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutical acceptable salts thereof for the treatment, preferably topically, of pruritus. In a method according to the present invention the NSAID or its pharmaceutical acceptable salt is administered, preferably topically, to a patient suffering from pruritus. Preferably the patient comprises an mammal, more preferably a human being. Preferably the NSAID or its pharmaceutical acceptable salt is applied directly to the affected area to achieve an anti-pruritic response and is present in an anti-pruritically effective amount.

Bendazac has the chemical name {[1-(phenylmethyl)-1*H*-indazol-3-yl]oxy}-acetic acid and is a known anti-inflammatory agent.

Benzydamine has the chemical name *N*,*N*-dimethyl-3-{[1-(phenylmethyl)-

1*H*-indazol-3-yl]oxy}-1-propanamine and is a known anti-inflammatory, analgesic and anti-pyretic agent.

Diclofenac has the chemical name 2-[(2,6-dichlorophenyl)amino]benzene acetic acid and is a known anti-inflammatory agent.

Fenbufen has the chemical name γ-oxo-3-(1,1'-biphenyl)-4-butanonic acid and is a known anti-inflammatory agent.

Indomethacin has the chemical name 1-(4-chlorobenzoyl)-5-methoxy-2-methyl--1*H*-indole-3-acetic acid and is a known anti-inflammatory, analgesic and anti-pyretic agent.

Ketoprofen has the chemical name 3-benzoyl-α-methyl-benzeneacetic acid and is a known anti-inflammatory and analgesic agent. It has one chiral centre (an asymmetrically substituted carbon atom).

Naproxen has the chemical name 6-methoxy-α-methyl-2-naphthaleneacetic acid and is a known anti-inflammatory, analgesic and anti-pyretic agent. It has one chiral centre (an asymmetrically substituted carbon atom), the S enantiomer being a preferred form of this drug.

Piroxicam has the chemical name 4-hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide and is a known anti-inflammatory agent.

Sulindac has the chemical name 5-fluro-2-methyl-1-(p-methylsulpinylbenzyl idene)inden-3-ylacetic acid and is a known anti-inflammatory agent.

Some of the specified NSAIDs described herein which are acids may form salts with organic or inorganic bases. Particularly suitable salts of the specified

NSAIDs comprise alkali metal salts (for example sodium and/or potassium salts), alkaline earth metal salts (for example magnesium and/or calcium salts), aluminium salts, ammonium salts, salts of suitable organic bases (for example salts of alkylamines and/or N-methyl-D-glutamine), salts of amino acids (for example salts of arginine and/or lysine). The NSAID salts also include all enantiomeric salts formed with pharmaceutically acceptable chiral acids and/or bases and/or any mixtures of enantiomers of such salts (for example (+) tartarates, (-) tartarates and/or any mixtures thereof including racemic mixtures). A preferred salt of the specified NSAIDs is the sodium salt.

Acid and/or base addition salts formed between the specified NSAIDs and the aforementioned bases may be generally expected to be soluble in water and/or hydrophillic organic solvents (for example ethanol) and therefore be of particular utility in the treatment of pruritus. Such salts may also be expected to have higher melting points compared to the corresponding NSAID.

References herein to NSAID salts include all salts of the specified NSAIDs which are pharmaceutically acceptable (i.e. non-toxic at therapeutically effective doses) and are present in amounts sufficient to give an anti-pruritic response. Some of these NSAID salts may also exist as racemates, separate enantiomers and/or mixtures thereof. Reference herein to NSAID salts include their racemates, separate enantiomers or any mixtures thereof of all pharmaceutically acceptable NSAID salts present in an amount sufficient to give an anti-pruritic response. The NSAID salts provided they are pharmaceutically acceptable, may be used in to treat pruritus in place of the corresponding NSAID.

Certain of the specified NSAIDs may exist as one or more stereoisomers (for example enantiomers, diastereoisomers, geometric isomers, tautomers, conformers and/or combinations thereof if possible within the same molecular

moiety). References herein to NSAIDs include all their pharmaceutically acceptable stereoisomers and/or any mixtures thereof.

Certain of the specified NSAIDs have a structure such that they are not superimposable on their mirror image (for example compounds with one or more chiral centres such as ketoprofen and naproxen) and thus exist as different enantiomeric forms which may or may not be optically active. Thus, for example NSAIDs in the substituents at a carbon atom are all different, contain a chiral centre at the asymmetrically substituted atom. NSAIDs that contain a single chiral centre may exist as two enantiomeric forms. The absolute configuration at a chiral centre may be denoted by the prefixes R or S. Alternatively if the absolute configuration at a chiral centre has yet to be determined, individual enantiomers may be distinguished by the prefixes (+) or (-) according to the direction of rotation of the plane of polarised light passed through a sample of the enantiomer. References herein to NSAIDs include all their pharmaceutically acceptable enantiomerically pure enantiomers, such enantiomers being substantially free (i.e. associated with less than about 5%) of their optical antipodes and/or any mixtures of such enantiomers (for example racemic mixtures and/or all other mixtures of enantiomers).

Certain of the specified NSAIDs may exist as one or more stable conformational forms. Torsional asymmetry in the NSAIDs may arise from strain in a ring system and/or from restricted rotation about an asymmetric single bond (for example because of steric hindrance) and may permit separation of different conformers. Thus NSAIDs which comprise different, bulky groups near to an asymmetric single bond (about which there is restricted rotation due to steric hindrance between the bulky groups) may exist as different, stable, staggered rotamers which may be separable. Reference herein to NSAIDs include all their pharmaceutically acceptable conformers and/or any mixtures thereof.

Certain of the specified NSAIDs and/or their salts may exist as one or more zwitterionic forms. Thus, for example, NSAIDs which comprise two centres of ionic charge and may exist as zwitterions. Reference herein to NSAIDs include all their pharmaceutically acceptable zwitterions and/or any mixtures thereof.

Certain of the specified NSAIDs may exist as one or more polymorphic forms (for example one or more crystalline forms, amorphous forms, phases, solid solutions and/or mixtures thereof). Reference herein to NSAIDs include all their pharmaceutically acceptable polymorphic forms and/or any mixtures thereof.

Certain of the specified NSAIDs may exist in the form of one or more complexes (for example chelates, clathrates, interstitial compounds, ligand complexes, organometallic complexes and/or solvates) which may be formed with a pharmaceutically acceptable substrate in which the NSAID and/or the substrate may act as a ligand (for example solvates formed from one or more pharmaceutically acceptable solvents [such as water]). Complexes may be non-stoichiometric (for example the degree of solvation may be non-stoichiometric). NSAIDs may exist as solvates (for example if the solvent is water the hydrates may be hemihydrates, monohydrates and/or dihydrates) or in an unsolvated form (for example an anhydrous form). Reference herein to NSAIDs include all their pharmaceutically acceptable complexes (including solvates) and/or any mixtures thereof.

The anti-pruritic activity of the specified NSAIDs and/or their pharmaceutically acceptable salts may be demonstrated by means of tests on animals, including human beings. Thus one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutical acceptable salts thereof are useful in the treatment of pruritus in animals, preferably human beings. Preferably the specified NSAIDs and/or their pharmaceutically acceptable salts are

administered topically, more preferably to an itchy site on the outer coat of an animal (such as fur, hide, pelt and/or skin), more preferably a mammal, most preferably human skin.

The precise amount of the specified NSAIDs and/or their pharmaceutically acceptable salts which may be administered to a patient to treat pruritus will depend on a number of factors, for example the severity of the condition, the animal being treated and the age and past medical history of the patient, and will lie within the sound discretion of any administering veterinary, physician, pharmacist and/or other medical practitioner. However a suitable daily dose (given in a single dose or in divided doses at one or more times during the day) of each specified NSAID and/or their pharmaceutically acceptable salts for administration to animals, preferably human beings, to treat pruritus may be generally as follows for each of the specified NSAIDs: bendazac from about 0.1 mg to about 2000 mg, preferably from about 1.5 mg to about 1500 mg; benzydamine from about 0.1 mg to about 400 mg, preferably about 4.5 mg to about 200 mg; diclofenac from about 0.1 mg to about 300 mg, preferably about 25 mg to about 75 mg; fenbufen from about 0.1 mg to about 1800 mg, preferably from about 300 mg to about 900 mg; indomethacin from about 0.1 mg to about 400 mg, preferably from about 25 mg to about 200 mg; ketoprofen from about 0.1 mg to about 600 mg, preferably from about 25 mg to about 200mg; naproxen from about 0.1 mg to about 2500 mg, preferably from about 250 mg to about 500 mg; piroxicam from about 0.1 mg to about 100 mg, preferably from about 5 mg to about 40 mg and sulindac from about 0.1 mg to about 1000 mg, preferably about 200 mg to about 400 mg.

As will be appreciated by the person skilled in the art, pruritic symptoms may occur on normal and abnormal skins and may be caused by a number of metabolic pathways (reference is made to R. Winkelmann, Medical Clinics of North America, Vol. 66, No 5, September 1982). Some pruritic conditions may arise from one or both of the following non-prostaglandins mechanisms, namely

via histamine and serotonin production. Examples of causes of pruritus in humans (and possibly other animals) include one or more of any of the following:

induction by UV-radiation (for example sunburn);

external non-UV stimuli (for example contact with fibres [such as wool and/or synthetic fibres], aqueous contact [aquagenic pruritus] and/or cholinergic pruritus [related to heat and/or exercise]);

enteral and/or parenteral contact with histamine-producing substances (for example food substances and/or plants);

administration of drugs (for example opiates, barbiturates and/or salicylamilides);

toxic products (for example bile salts and/or urea) released due to failure of body organs (for example kidney and/or liver failure);

pruriginous disease (for example leprosy);

stimulation of (or other changes in) nerve endings, fibres and/or receptors in the skin;

psychogenic causes; and

xerosis (abnormal dryness) of the skin in the elderly.

Pruritus, or itching, may be classified amongst the following conditions (see Winkelmann 1982):

Physiologic itch is a short-lived cutaneous response to the usual environmental and body stimuli which may or may not elicit scratching, and is to be distinguished form tickle which is considered to be moving touch plus its affective response.

Pathologic itch is an intense cutaneous discomfort occurring with pathologic change in the skin or body which usually elicits vigorous scratching or other effort at relief.

Spontaneous itch is itching unrelated to pathologic change in the skin or cutaneous nerves and elicited by toxic or metabolic change within the body. This may be physiologic or pathologic itch.

Focal itch is a locus of pathologic itching caused by cutaneous nerve or other tissue change.

Scattered itch is multiple, distant areas of pruritus and may exist in the skin following an itching excitation in only one skin area.

Referred itch is a more recent name for scattered itch but often in the same dermatome.

Conversion itch is a condition described in 1964 by Winkelmann to account for the change of a usual sensory experience into itch, as touch or tickle to itch in atopic skin of normal appearance.

Itchy skin is an area of hyper-responsiveness to stimuli for itch about a primary stimulus zone for itch or a primary skin inflammation. This is analogous to the hyperalgesic zone about a skin spot stimulated to pain.

Central neural itch is itching stimulated and/or maintained by the central nervous system. Cutaneous changes are not primary.

In addition various diseases or disorders have pruritus as one of their main symptoms. They may comprise any of the conditions listed below:

Dermatitis, or eczema, is a superficial inflammation of the skin, and is characterised by vesicles (when acute), redness, oedema, oozing, crusting, scaling and usually itching.

Contact dermatitis is an acute or chronic inflammation of the skin which is often sharply demarcated. It is produced by contact between the skin and some substance or stimulus to which the skin is sensitive, for example those described above.

Atopic dermatitis is a chronic, itching superficial inflammation of the skin usually occurring in individuals with a personal family history of allergic disorders (for example hay fever, asthma) due to an inherited state of hypersensitivity. It is also known as infantile eczema as it often starts in infants at about the age of 3 to 4 months.

Seborrhoeic dermatitis is an inflammatory scaling disease of the scalp, face and occasionally other areas of the body which produces variable amounts of itching.

Nummular dermatitis is a chronic dermatitis characterised by inflamed, coin-shaped, vesicular, crusted, scaly and usually pruritic lesions.

Pompholyx is a chronic condition characterised by deep-seated itchy vesicles on the palms, sides of the fingers and soles of the feet. When it occurs on the fingers and hands it is known as cheiropompholyx. On the toes and feet it is known as podopompholyx.

Generalised exfoliative dermatitis is a severe widespread erythema and scaling of the skin. Itching may be severe or absent.

Localised scratch dermatitis is a chronic, superficial, pruritic inflammation of the skin.

Impetigo is a superficial, vesiculopustular skin infection seen chiefly in children. It is usually caused by the staphylococcus aureus. Itching is common and

scratching may spread the infection, as the discharge from the vesicles is infectious.

Ecthyma is an ulcerative form of impetigo.

Scabies is a transmissible, parasitic skin infection caused by the mite Sarcoptes Scabies. The condition is characterised by superficial burrows, intense pruritus and secondary skin infection. The intense itching of this condition gives scabies its popular name of `itch'.

Pediculosis is infestation by lice.

Urticaria (otherwise known as hives or nettle rash) results in local wheals and erythema in the dermis. Food allergy is a common cause of urticaria, which is generally agreed to be an allergic reaction on behalf of the sufferer to some substance to which they are hypersensitive. Pruritus is generally the first symptom, occurring shortly after exposure to the substance which causes the condition.

Lichen simplex and lichen planus are recurrent, pruritic, inflammatory eruptions characterised by small, discrete, angular papules that coalesce into rough scaly patches with consequent thickening and hardening of the skin.

Miliaria (prickly heat) is an acute, inflammatory, pruritic eruption due to retained extra-vasated sweat, often affecting people travelling to the tropics. A similar condition can occur in some people upon getting warm in bed or at the start of spring or autumn when changes in the size of blood vessels in the skin take place.

Dermatitis herpetiformis is a chronic eruption characterised by clusters of intensely pruritic vesicles, papules and urticaria-like lesions.

A very aggravated form of itching may occur at the anus, known as pruritus ani. This is often caused by threadworms. An equally troublesome form of itching known as pruritus vulvae can occur around the vagina and may be associated with excessive vaginal discharge.

Elderly humans often suffer from pruritus as the skin becomes thin and inelastic. This is commonly seen as cold weather itch on the legs of old people when their skin becomes drier in the colder weather. Pruritus in the elderly may be due to a primary skin disease, a systemic disease or may have multifactorial or idiopathic causes. It is believed that xerosis is the most common cause of itching in the elderly.

Other more systemic conditions that may give rise to pruritus comprise obstructive biliary disease, uraemia, lymphomas, leukaemias, polycythemia rubra vera and diabetes mellitus. Jaundice and glomerulo-nephritis may also be accompanied by itchiness in a milder degree.

Patients that may be treated by the methods and/or with the compositions described herein, comprise any animals capable of itching, preferably mammals, more preferably human beings. The term 'animal' as used herein should be construed as including human beings as well as non-human animals. Non-human animals that may be treated for pruritus as described herein comprise those commonly encountered as domestic pets (for example cats, dogs, rabbits and/or guinea pigs); those used commercially (for example livestock [such as pigs, cows and/or sheep] and/or working animals [such as horses]) and/or those animals kept in zoos or wildlife parks (for example zebra, lions and/or elephants). Patients which may be treated for itch as described herein should not be considered limited to those animals mentioned above. In principle any animals including non-mammals (for example reptiles and/or birds) may be treated. Aquatic animals (for example fish and/or aquatic mammals)

may also be treated with a topical formulation of the invention that is waterproof or water resistant. It may also be possible to treat wild animals in their natural environments using the methods and compositions of the present invention as part of a more general management strategy, for example in a game reserve or national park.

Methods and/or compositions of the present invention may be useful in preventing non-human patients from scratching an itchy site (such as on their coat, fur, hide. pelt and/or skin). Scratching may be therapeutically undesirable as it may cause damage or aggravate any underlying condition, and/or may be cosmetically undesirable as it may blemish the skin. Inhibition of scratching may be particularly important (either as a method of therapy or as a non-therapeutic cosmetic treatment) on non-human animals with a high cultural and/or economic value (for example endangered species bred in captivity for possible re-introduction into the wild [such as pandas], highly valuable animals [such as racehorses] and/or animals [such as mink] which are bred for their coat e.g. to produce leather or fur).

A still further aspect of the present invention also provides for use of one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof, in the preparation of a medicament for treating pruritus. Preferably the medicament is a topically medicament.

As mentioned above, pruritus often arises as symptom produced by an underlying condition. Use of a topical medicament of the present invention may alleviate pruritic symptoms with or without a therapeutic effect on any underlying condition.

Itching may induce scratching of the skin. Scratching is often therapeutically undesirable because it may aggravate the pruritus and/or any underlying

condition but also may be cosmetically undesirable, for example, because it may produce or worsen unsightly blemishes on the skin. Relief from itching sufficient to reduce and/or eliminate the urge to scratch may produce a cosmetically desirable effect independent of any curative and/or other therapeutic effect on the pruritus and/or any underlying condition. For example, if the degree of scratching required to produce an undesirable therapeutic effect is significantly greater than that required to produce a cosmetically undesirable effect, then treatment to reduce the urge to scratch may not necessarily have a concurrent therapeutic effect. Thus application of compositions of the present invention may have utility as a non-therapeutic method of cosmetic treatment to prevent disfigurement by suppressing the urge to scratch an itchy site.

Therefore the present invention further provides a non-therapeutic method of cosmetic treatment for inhibiting the urge to scratch the skin elicited by itching, comprising applying topically to the itchy site a composition comprising one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof. The cosmetic treatment of the present invention acts to reduce the degree of scratching by an amount sufficient to result in a corresponding reduction and/or elimination of the cosmetically undesirable effects caused by such scratching. Compositions suitable for use in such a topical treatment may comprise those compositions known to persons skilled in the art of cosmetics formulation and/or the pharmaceutical compositions described herein.

The method of therapy, treatment (including cosmetic treatment), use and/or compositions described herein may be applied in conjunction with any other compatible therapy, treatment (including cosmetic treatment) and/or composition also for the treatment (including cosmetic treatment) of pruritus, and/or the treatment of any other condition (for example any condition which may be the underlying cause of the pruritic symptoms).

The amount of the one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof, in a formulation should be such that an anti-pruritically effective amount of the specified NSAIDs and/or their pharmaceutically acceptable salts are delivered to the patient. If the formulation is applied topically such an amount should be delivered during the period of time for which the topical formulation is intended to be on the patient. A topical formulation of the present invention should be capable of remaining on the patient for at least that period of time necessary to produce an effective anti-pruritic response in the area treated (e.g. the itchy skin). For any given formulation of the invention the delay before onset of any anti-pruritic effect depends on many factors including the nature of the pruritus, the area and type of skin being treated and the species and age of patient, as well as the nature of the formulation. Typically for an adult human patient, the delay before onset of an anti-pruritic effect may be from about a few seconds to about an hour or more, more usually from about one to twenty minutes.

A further aspect of present invention also provides a pharmaceutical composition having anti-pruritic activity when administered to a patient in need thereof, the composition comprising one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof as an anti-pruritic agent, preferably the only anti-pruritic agent.

The present invention further provides a method of treating pruritus using the compositions described herein.

Preferably compositions of the present invention comprise the anti-pruritic agent in an amount from about 0.01% to about 25 % by weight, more preferably from about 0.5 % to about 15 % by weight, most preferably from about 0.5 % to

about 10 % by weight of the composition. Advantageously compositions of the present invention comprise the anti-pruritic agent in an amount from about 2.5 % to about 10 % by weight of the composition.

Formulations used in methods of, or as compositions of, the present invention may provide a local and/or systemic therapeutic and/or cosmetic effect, and may be administered in a prophylactic manner, for example to prevent the onset of pruritus and/or to prevent the urge to scratch the skin. Such formulations, or compositions, may be formulated in a manner known to those skilled in the art to give a controlled release, for example rapid release or sustained release, of the NSAID and/or their pharmaceutically acceptable salt or salts.

It will readily be understood that in the formulations of the present invention described hereinafter, the NSAID ingredient may be replaced or supplemented by any of their pharmaceutically acceptable salts compatible with the ingredients used in the formulation.

Suitable compositions of the present invention, or formulations for use in methods of the present invention, which are especially suitable for topical administration may comprise a matrix in which the NSAID is dispersed so that the NSAIDs are held in contact with the skin in order to administer the compound or compounds transdermally. Suitable matrices for topical application may comprise topical delivery devices such as cataplasms, poultices, patches or impregnated bandages.

A composition suitable for transdermal delivery may be prepared by mixing the NSAID with a topical vehicle (for example a mineral oil, petrolatum, light liquid paraffin and/or a wax [such as paraffin wax and/or beeswax]) together with a potential transdermal accelerant such as dimethyl sulphoxide and/or propylene glycol. Alternatively, the NSAID may be mixed with and/or dispersed in, a pharmaceutically acceptable foam, paste, salve, lotion, cream, ointment,

emulsion and/or gel base, and/or applied in the form of a spray. A suitable cream may be prepared by incorporating the NSAID in petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using a surfactant. A suitable ointment may be prepared by mixing the NSAID with a mineral oil, petrolatum and/or a wax (for example paraffin wax and/or beeswax). A suitable gel may be prepared by mixing the NSAID with a topical vehicle comprising a gelling agent (for example basified Carbomer BP) in the presence of water.

Preferably compositions of the present invention comprise a pharmaceutically acceptable diluent or carrier, more preferably an aqueous solvent, most preferably purified water.

Preferably compositions of the present invention also comprise a thickening agent in an amount from about 0.1% to about 10% by weight, more preferably from about 0.2% to about 5% by weight, most preferably from about 0.5% to about 3% by weight of the composition. The thickening agent may comprise hydroxyethyl cellulose, and/or a carboxyvinyl cross polymer (for example that available commercially from B.F. Goodrich Limited under the trade name Carbopol 980NF) and a pH adjusting agent as necessary to activate the thickening agent.

Preferably compositions of the present invention further comprise a pH adjusting agent, more preferably a basic pH adjusting agent. Preferably the pH adjusting agent is present in an amount which is sufficient to activate the thickening agent, if present, and which will keep the pH of the composition within a pharmaceutically and cosmetically acceptable range that will not damage the skin. More preferably the pH of the composition is from about 5.0 to about 9.0. Subject to the aforementioned, the pH adjusting agent, is preferably present in an amount from a trace amount to about 15% by weight, more preferably from about 0.01% to about 12% by weight, most preferably from about 0.1% to about 10% by weight of the composition. The pH adjusting

agent may comprise sodium citrate, sodium hydroxide, potassium hydroxide and/or N,N,N',N'-tetrakis(2-hydroxypropyl)ethylenediamine (available commercially under the trade name Quadrol).

Compositions of the present invention may additionally comprise a preservative. Preferably the preservative is present in an amount from a trace amount to about 5% by weight, more preferably from about 0.1% to about 3% by weight, most preferably from about 0.5% to about 2% by weight of the composition. The preservative may comprise bronopol, sodium dehydroacetate, polyhexamethylenebiguanide hydrochloride, isothiazolone diazolidinylurea and/or 2-phenoxyethanol (available commercially under the trade name Phenoxetol Nipa).

Compositions of the present invention may further comprise a humectant to improve the feel of the composition on the skin. Preferably the humectant is present in an amount from about 1% to about 30% by weight, more preferably from about 5 to about 20% by weight, most preferably from about 7% to about 15% by weight of the composition. The humectant may comprise a glycol which is defined herein as one or more organic compounds each having at least two hydroxy groups preferably on adjacent atoms. More preferably the glycol may comprise polyethylene glycol, glycerin and/or any mixture of these.

If a composition of the present invention is a gel, such a gel may be a clear gel comprising a clarifying agent, preferably a denaturated alcohol, more preferably denaturated ethanol. Preferably the clarifying agent is present in an amount from about 5% to about 60% by weight of the composition.

If a composition of the present invention is an emulsion, such an emulsion may be either an oil-in-water or a water-in-oil emulsion.

The oil phase of an emulsion that may comprise a composition of the present invention may comprise one or more of the following ingredients and/or any mixture of these:

hydrocarbon oils (for example paraffin and/or mineral oils);

waxes (for example beeswax and/or paraffin wax;

natural oils (for example sunflower oil, apricot kernel oil, shea butter and/or jojoba oil);

silicone oils (for example dimethicone, cyclomethicone and/or cetyldimethicone);

fatty acid esters (for example isopropyl palmitate and/or isopropyl myristate); and

fatty alcohols (for example cetyl alcohol and/or stearyl alcohol);

In a preferred oil-in-water emulsion that may comprise a composition of the present invention, the oil phase comprises from about 5% to about 30% by weight, more preferably from about 10% to about 20% by weight of the composition.

Emulsifiers that may be used in a composition of the present invention may be any emulsifiers known in the art for use in water-in-oil or oil-in-water emulsions. Those compositions of the present invention that are emulsions can be prepared by using an emulsifier and/or a mixture of emulsifiers selected from known emulsifiers acceptable for use in topical compositions which may comprise one or more of the following ingredients and/or any mixtures of these.

sesquioleates (for example sorbitan sesquioleates [such as that available commercially from ICI under the trade name Arlacel 83]);

ethoxylated esters of derivatives of natural oils (for example polyethoxylated esters of hydrogenated castor oils [such as that available commercially from ICI under the trade name Arlacel 989]);

silicone emulsifiers (for example silicone polyols [such as those available commercially from Th. Goldschmidt AG under the trade name ABIL WS05 and from Dow Corning under the trade designation Silicone Fluid 3225C]);
fatty acid soaps (for example potassium stearate);
ethoxylated fatty alcohols (for example those available commercially from ICI under the trade name Brij and from Croda under the trade name Cithrol GMS A/S);
sorbitan esters (for example those available commercially from Croda under the trade name Crill);
ethoxylated sorbitan esters (for example those available commercially from ICI under the trade name Tween);
ethoxylated fatty acid esters (for example ethoxylated stearates [such as that available commercially from ICI under the trade name Myrj]);
ethoxylated mono-glycerides, di-glycerides and/or tri-glycerides (for example those available commercially from Alfa Chemicals under the trade name Labrafil); and
ethoxylated fatty acids (for example those available commercially from Alfa Chemicals under the trade name Tefose).

The amount of emulsifier optionally present in a water-in-oil emulsion that may comprise a composition of the present invention is preferably in the range from about 0.1% to about 20% by weight of the composition.

The amount of emulsifier optionally present in an oil-in-water emulsion that may comprise a composition of the present invention is preferably in the range from about 0.1% to about 20% by weight of the composition.

If a composition of the present invention is other than an emulsion, an emulsifying ingredient and/or surfactant (for example one of those emulsifiers listed above), may still be present (for example in the amounts given above) as

a surface active agent to promote greater therapeutic activity in the composition when it is applied topically.

The compositions of the present invention may additionally comprise one or more other component, components and/or any mixture of these, which will be well known to those skilled in the art and may be selected from:

emulsion stabilisers (for example stearyl alcohols and/or cetyl alcohols) and/or emulsion stabilising salts (for example sodium chloride, sodium citrate and/or magnesium sulphate), preferably in an amount from about 0.1% to about 5% by weight of the composition;

sequestrants (for example tetra sodium ethylene diamine tetra acetate dihydrates [such as that available commercially from Rhône Poulenc under the tradename Sequestene NA4]), preferably in an amount from a trace amount to about 1% by weight of that composition;

anti-oxidants (for example DL tocopherol acetate and/or butylated hydroxytoulene), preferably in an amount from about a trace amount to about 1% by weight of the composition;

emollients (for example mineral oil, polymethylsiloxane, sweet almond oil, petroleum jelly, isopropyl myristate and/or triglycerides of fatty acids [such as lauric triglyceride, capric/caprylic triglyceride, and/or mixed triglycerides {e.g. that available commercially from Huls UK Ltd under the trade name Miglyol 810}]), preferably in an amount from about 0.1% to about 30% by weight of the composition;

moisturisers (for example D-panthenol), preferably in an amount from a trace amount to about 1% by weight of the composition;

film formers to assist spreading on the surface of the skin (for example alkylated polyvinylpyrrolidone), preferably in an amount from a trace amount to about 1% by weight of the composition; and

perfumes and/or colouring.

The invention will now be illustrated with reference to the following non-limiting Examples, of topical compositions suitable for use in the present invention in which all percentages given are by weight of ingredient per total weight of the composition (known herein as '% w/w'). The NSAID ingredient in each of the Examples may be any of bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac or their pharmaceutically acceptable salts. In the Examples 2-phenoxyethanol, which is a preservative, is available commercially under the tradename Phenoxetol Nipa; carboxyvinyl crosspolymer, which is a thickening agent, is available commercially from B.F. Goodrich Limited under the tradename Carbopol 980 NF; N,N,N',N'-tetrakis (2-hydroxypropyl)ethylene diamine, which is a basic pH adjusting agent, is available commercially under the tradename Quadrol; and ethoxylated fatty alcohol, which is a surface active agent, is available commercially from ICI under the tradename Brij 92.

Example 1

Ingredient	% w/w
NSAID	5.0
Polyethylene glycol 300 BP (humectant)	10.0
2-Phenoxyethanol (Phenoxetol Nipa)	1.0
Carbovinyl crosspolymer (Carbopol 980NF)	0.5
Sodium hydroxide BP pellets (pH adjuster)	0.085
Purified water BP (diluent)	to 100

The ingredients above can be mixed together to form an opaque gel composition suitable for topical application to itchy skin.

Example 2

Ingredient	% w/w
NSAID	2.5
Carboxyvinyl crosspolymer (Carbopol)	2.0
Denatured ethanol (clarifying agent)	5.0
Sodium hydroxide (pH adjuster)	1.525
2-Phenoxyethanol (Phenoxetol)	1.0
Purified water (diluent)	to 100

The ingredients above can be mixed together to form an opaque gel composition suitable for topical application to itchy skin.

Example 3

	% w/w
NSAID	2.5
Polyethylene glycol (humectant)	10.0
2-Phenoxyethanol (Phenoxetol)	1.0
Carboxyvinyl crosspolymer (Carbopol)	0.5
Sodium hydroxide (pH adjuster)	0.085
Purified water (diluent)	to 100

The ingredients above can be mixed together to form an opaque gel composition suitable for topical application to itchy skin.

Example 4

Ingredient	% w/w
NSAID	2.5
Carboxyvinyl crosspolymer (Carbopol)	2.0
Denatured ethanol (clarifying agent)	50.0
Polyethylene glycol (humectant)	5.0
Glycerin (humectant)	5.0
Purified water (diluent)	to 100

The ingredients above can be mixed together to form an opaque gel composition suitable for topical application to itchy skin.

Example 5

Ingredients	% w/w
NSAID	10.0
Denatured ethanol (clarifying agent)	40.0
Carboxyvinyl crosspolymer (Carbopol)	2.6
N,N,N',N'-tetrakis (2-hydroxypropyl)ethylene diamine [Quadrol]	9.0
Propylene glycol (humectant)	2.0
Ethoxylated fatty alcohol (Brij 92)	2.0
Purified water (diluent)	to 100

The ingredients above can be mixed together to form an opaque gel composition suitable for topical application to itchy skin.

CLAIMS

1. Use of one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof, as an anti-pruritic agent for the treatment of pruritus

2. Use as claimed in claim 1, the NSAID and/or its salt being applied topically to a patient in need thereof.

3. Use as claimed in either preceding claim, in which the patient is a human being.

4. Use of one or more NSAIDs selected from sulindac, fenbufen, naproxen, diclofenac, ketoprofen, indomethacin, piroxicam, benzydamine, bendazac and any pharmaceutical acceptable salts thereof, in the preparation of a medicament for treating pruritus.

5. A method of treating pruritus in animals using a pharmaceutical composition comprising as an anti-pruritic agent one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof.

6. A method of treatment as claimed in claim 5, in which the composition is applied topically to an animal in need thereof.

7. A method of treatment as claimed in either claim 5 or 6, in which the animal is a human being.

8. A non-therapeutic method of cosmetic treatment for inhibiting in a subject the urge to scratch the skin elicited by itching, comprising applying to a subject in need thereof, a pharmaceutical composition comprising one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof, as anti-pruritic agent.

9. A method of cosmetic treatment as claimed in claim 8, in which the composition is applied topically to the subject.

10. A method of cosmetic treatment as claimed in claim 9, in which the subject is a human being.

11. A pharmaceutical composition having anti-pruritic activity when administered to a patient in need thereof, the composition comprising as an anti-pruritic agent one or more NSAIDs selected from bendazac, benzydamine, diclofenac, fenbufen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac and any pharmaceutically acceptable salts thereof.

12. A composition as claimed in claim 11 which is suitable for topical administration to a patient in need thereof.

13. A composition as claimed in any of claims 11 or 12, in which the anti-pruritic agent comprises from about 0.01% to about 25% by weight of the composition.